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Re:	SN 09/964,120		

Urgent **For Review** **Please Comment** **Please Reply** **Please Recycle**

Message

Attached please find Response E to the Office Action dated October 31, 2003, including newly submitted claims33-41:

Application No. 09/964,120
Inventor: Marvin L. Schilling et al
Filed: 9/25/2001
For: Method for Producing Biologically Active Products

Examiner Sharmila S. Golumudi

Art Unit 1616

Bernd W. Sandt

.IN THE UNITED STATES PATENT & TRADEMARK OFFICE6

Applicant: Marvin L Schilling & Richard D. Farfard

Serial No: 09/964,120

Filed: 09/25/01

For: Method for producing Biologically Active Products

Group Art Unit:1616 Examiner: Sharmila S Gollamudi

Hon. Commissioner of Patents
& Trademarks,
Washington, D.C. 20231

Sir,

RESPONSE E

In response to the Office Action dated October 31, 2003 please cancel claims 18 to 32 and add claims 33 to 41 in the subject application.

The applicants wish to thank the Examiner for the telephone interview on December 10, 2003. The Examiner indicated her concern that using salt to stabilize food was old and well known. However applicants believe that such salting generally is done after cooking and even if done during cooking does not involve extensive dehydration. However even if that were the case cooking temperatures are much higher than the temperatures employed in applicants invention, which are not higher than temperature conditions experienced in nature. The Examiner also believed that one could properly combine the Japanese patent with the Ueno reference and thereby make obvious all of the elements of applicants' invention. Although applicants disagree on that point, it is believed that the amended claims overcome even the combination of these references in

that they now differ from the references in the material employed in the dehydration, spell out that the original structure of the proteins in the cartilage is unaffected and in the large amount of salt employed and retained by the product.

Applicants have limited their claims to collagen II-containing cartilage materials. Cartilage materials are recognized as being the only material in living organisms that contain more than a trace of collagen II and thus would be suitable for therapeutic applications based on collagen II. The principal basis for the invention is the discovery that significant amounts of an ionic salt stabilize the insoluble structure of the collagen II containing material and thus retain the therapeutic value of the original cartilage. Although some form of denaturation may be prevented in the references cited it is not clear that the same denaturation is involved since different proteins are involved in each of the references. Applicants have further specified the nature of the end product in two ways to distinguish over references that modify the protein before hydration and that may use minimal concentrations of a salt. Support for the limitations are found on page 7 line 6 to 23 and page 5, line 28 to page 6 line 7. As amended it is submitted that the claims are now patentable over the art cited by the Examiner.

In the event that the amended claims still are not considered to be allowable, applicants traverse the rejection as set forth in the Office Action.

The Examiner rejected claims 18-19, 21-22 and 27 as being unpatentable over JP 59-088065 in view of (Ueno et al 4,789,497). The amended claims are now believed to be patentable over this combination.

JP discloses the preparation of a paste from ground bone and marrow. (Bone consists of 65-70% of an inorganic component, hydroxyapatite and 35 % of an organic component that is 95% collagen I, a fibrous protein very different from collagen II. Marrow is principally blood and fat.) The patent discloses that the bone and marrow are cut into relatively large pieces and washed with a solution of hypochlorite. The resulting particulate is then combined with a solution of soy lecithin and then finely ground with the grinding machine placed inside a freezer at -15^0 C to prevent degeneration as a result

of heating. This is the only step disclosed as requiring protection since none of the other steps is conducted at such temperatures. The product is then washed with water and dehydrated by means of a centrifugal separator. There is no disclosure as to either the extent of the dehydration or the temperature conditions under which such dehydration is carried out. After the dehydration a second solution of lecithin is combined with the finely ground material and results in a paste having a water content of 72%. The paste can be freeze-dried or dried with hot air but no conditions are shown as to how that is to be accomplished nor is the desirability to prevent denaturation mentioned. Thus it is only in the pulverization step that the patent warns against denaturation. This step does not involve dehydration. The dehydration step involved in the JP patent does not require it to be conducted at temperatures, which prevents thermal denaturation. There is no basis to extend the denaturation requirement of the pulverizing step to the dehydration step.

The Ueno patent relates to pressed fish meat. Fish meat with a water content of 94 % or more is washed with an aqueous solution containing a mixture of sodium chloride and an alkaline earth metal salt in a concentration of 0.005 to 0.5 wt %. The purpose of the washing is to prevent denaturation during freezing and the purpose of the addition of the salts to the wash water is top prevent the elution of protein contained in the fish meat into the wash water. The wash water itself elutes certain "factors" (undefined) which can cause the denaturation of the fish during the freezing process. Thus the fish meat is changed prevent denaturation. The resulting water swollen fish meat is then dehydrated to remove such added water by first separating the wash water on a rotary sieve and then passing the mixture through a screw press. The product has a water content in the range of 81 to 88 %. The resulting product can then be admixed with 3 % of sodium chloride and 5 % of potato starch and heated for 30 minutes in 90^0 C, (194^0 F), water to give a further product that has a water content in the range of 72 to 77 %.

Applicants submit that the combination of these two references is unsupported and unwarranted. The two references obviously relate to different substances, i.e., bone and marrow vs. fish meat, and there is no suggestion of any equivalency of the proteins involved in these two references or why preventing thermal denaturation has anything to

do with preventing denaturation resulting from freezing the product. The only denaturation prevention suggested by Ueno is through removal of components of the fish meat during washing. There is no concept of denaturation during drying through heating. On the contrary Ueno heats his material to a temperature of 90^0 C, (194^0 F) in water thus demonstrating that Ueno is neither concerned with dehydration nor with denaturation. The stabilization referred to by Ueno is to prevent proteins in the fish meat from eluting into the wash water thereby adversely affecting the mechanical properties of the product. Such stabilization can not be compared to stabilization against degradation of the protein. The JP patent discloses the use of lecithin as an additive whereas the Ueno reference uses a dilute salt solution. No equivalence of the two is suggested I either reference.

Furthermore there is no motive on the part of a person skilled in the art to use salt in the wash water of the JP process. The process as described in the Japanese patent must be assumed to produce a satisfactory process so why should anyone want to change it particularly since it involves a different product and procedure.

It is believed to be improper to just pick out a few sentences out of the reference without considering the context in which they are made. Applicants request that the combination of Ueno and the JP reference be withdrawn.

Nothing in the references furthermore relates to the dehydration of collagen II containing cartilage and the stabilization of the collagen II structure during dehydration by the addition of an ionizing salt to the cartilage itself in the significant amounts stated. Applicants' claims as now amended set forth the amounts of the ionizing salt required and the degree of dehydration as well as the temperature limit that must be maintained to prevent denaturation. No dehydration degree is set forth in the JP reference, although after the addition of minor amount of water the water content of the "dehydrated product is around 72 %indicating that the water content is not significantly reduce and probably involves only added water and not water contained in the original material. Ueno similarly reduces the water content by only a minor amount to between 70 and 88 %. Neither Ueno nor the JP teach the addition of an ionizing salt to the protein containing material itself and to be present during dehydration or resulting in a product having significant salt concentration. Washing the protein containing material with a very dilute

solution of an ionizing salt does not teach that even minor quantities of the salt are added to the protein itself and retained during the dewatering. There further is no suggestion of the numerical limits of applicants' claims in the references.

The Examiner correctly states JP discloses the mixing with soy lecithin and grinding at temperatures that do not degrade the protein. The temperature shown in the patent is -15^0 C The Examiner goes on to state that the product is then dried in hot air. That however only applies to a small part of the ground product. The major part of which is used as paste after mixing with additional lecithin solution which then contains more than 70 % of water. The reference does not teach that protein degradation should be avoided in the drying step for the minor product and the extension of that teaching to the drying step is unwarranted. The Examiner relies on the teaching of Ueno that washing removes factors that cause denaturation and that adding ionizable salts at the time of washing improves the dehydration. But preventing denaturation resulting from exposure to freezing temperatures and thereby improving mechanical properties is certainly not equivalent to any protein degradation that occurs as a result of excess heating. They are separate factors and there is no basis to equilibrate them or extend them to thermal dehydration. The Examiner then argues that the washing steps of the two references can be combined. Improvement in the properties as suggested by Ueno can be an improvement in mechanical or physical properties and not in molecular stability. The Examiner furthermore improperly expands the scope of each reference by ignoring the limitations of the references to the particular types of proteins involved.

In summary therefore the claims as currently worded are related to neither of the proteins disclosed in the references. Neither reference shows the addition of an ionizing salt to the protein itself and particularly not in the substantial concentrations set forth in the claims. Neither reference shows a dehydration to the dryness required by applicant's claims. None of applicants' basic elements can thus be found in the references, even if they could be combined.

Cancelled claims 20, 23-26 and 28-32 were rejected as unpatentable over JP 59-088065 in view of Ueno (4,789,497 and further in view of Puppolo (5,562,535)

Puppolo uses an azeotropic extraction of water with a hydrocarbon solvent such as benzene, toluene or heptane to remove water from treated shark cartilage, which had been treated with a dilute acidic solution of a proteolytic enzyme to remove protein and fat. The drying is accomplished by passing the mixture through a nozzle under pressure into a heated environment.

Applicants traverse the combination of these three references. All three relate to different proteins and there is no suggestion in any one of them as to the applicability to of the disclosed invention to any other type of protein. All three have different steps as pre-treatments. The JP patent mixes in lecithin and washes the bone and marrow with a hypochlorite solution. Ueno washes the fish meat with a solution of alkali and alkaline earth metal salts. Puppolo treats the shark cartilage with a protolytic enzyme which removes protein.. The dehydration method used in each of the three is different. Both Ueno and JP disclose different mechanical means to remove excess water and Puppolo uses an azeotropic extraction to remove the water. All three patents are limited to their particular technologies and there is no basis for adding any one feature of one process to any other. All three processes must be assumed to accomplish their intended results. What reason is there then to modify the disclosed technology JP, with elements from patents that relate to different proteins, employ different pretreatments and different dehydration techniques.

The MPEP clearly states (§ 2143) that there must be some suggestion or motivation either in the references or in the art to modify or combine the reference teachings and that there must be a reasonable expectation of success. Also the combination must teach all of the claim limitations. The Examiner can not rely on applicants' disclosure to provide the missing links to justify the combination, see *In re Vaeck* 947 F2d 488, 20 USPQ2d1438 (Fed. Cir. 1991). The diverse references cited by the Examiner contain no motivation or suggestion for combining them.

Furthermore even if combinable the combination fails to suggest all of the elements of the claims, particularly as amended. Not a single reference involves the dehydration of a collagen II containing cartilage in unmodified form. Puppolo comes

close but does not involve such in unmodified form. The protolytic type enzyme treatment removes protein and thus changes the nature of the cartilage. None of the references suggests combining large quantities of an ionizing salt with the cartilage particle.

The examiner argues that it would be obvious to combine the teachings of JP and Puppolo and use applicants' temperatures in JP's hot drying step. On what basis does the Examiner assume that the drying temperature employed by Puppolo for the protein remaining after proteolytic digestion in shark cartilage is applicable to the protein in bone. Furthermore on what basis can the Examiner assume that the temperatures used in an azeotropic extraction can be extended to the drying of a different protein in the absence of such organic solvent? Neither the materials nor the methods are the same thus no basis for an extension of the teachings of Puppolo to JP exists.

Cancelled Claims 18-31 were rejected as unpatentable under 35 USC § 103 as being unpatentable over Moore in view of Ueno et al (4,789,497) and Puppolo (5,562,535).

The Examiner correctly interprets Moore and recognizes that Moore does not add an ionizing salt to the cartilage. The examiner is in error, however in assuming that applicants add the salt to the antimicrobial solution. The salt is added to the cartilage. Ueno relates to washing fish meat with a solution containing an ionizing salt. The salt is added to prevent the elution of protein from the fish meat when compressed mechanically to reduce the excess water content. Furthermore it is not the addition of the ionizing salt that prevents denaturation but it is the washing itself that causes the removal of certain "factors" causing the denaturation of protein during freezing" (column 1 lines 16-23). On what basis would a person skilled in the art be motivated to extend the teachings Ueno to that of Moore which involve a different protein a different method of removing the water and a different type of denaturation. But of course even the combination would not teach the addition of the stated amounts of an ionizing salt to the cartilage. Puppolo involves still a different method of drying and would not suggest any temperature limitations or

operable temperatures for drying in the presence of large salt concentrations and in the absence of an organic solvent.

Applicants submit that the claims in amended form are patentable over the art and an allowance is requested.

Respectfully submitted,

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Certificate under 37 CFR 1.8

I hereby certify that a copy of the foregoing Response has been forwarded to Group Art Unit 1616 to the attention Examiner Sharmila S. Gollamudi by facsimile mail.

Date: 12/13/03

Signature